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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/943,777	10/03/1997	HENRIK STENDER		9688

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	31

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/943,777	Applicant(s) STENDER ET AL.	
	Examiner Jeffrey Fredman	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 37-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 37-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

1. The current case is a situation where the PTO mailed out both a letter of missing parts for the CPA along with the final rejection (without letting the examiner know). Since both clocks were concurrent, the final rejection is withdrawn and the current action is non-final. Consequently, the preliminary amendment which cancels claims 1-36 and replaces these claims with claims 37-47 is entered and the rejections which follow are addressed to these claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 37-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register:

December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass methods of detection of mycobacteria which comprise the use of a genus of nucleic acid probes which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID Nos. Thus, applicant has express possession of only 20 or so working examples, in a genus which comprises hundreds of billions of different possibilities. Here, no common element or attributes of the sequences are disclosed in the claims, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass any probes which function without any structural constraints. No written description of alleles, of upstream or downstream regions containing additional sequence, or of other variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516,

> 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the mycobacterial probes lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but fails to provide descriptive support for the generic claim to any PNA probe, for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely by its functional utility, as a probe.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise would function as mycobacterial probes. Therefore, the

claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 37-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al (U.S. Patent 5,541,308) in view of Hyldig-Nielsen et al (WO 95/32305).

Hogan teaches a method for detecting a mycobacterium target sequence (column 2) comprising: (1) contacting rRNA or rDNA in a sample with a nucleic acid probe, which probes comprise SEQ ID NO: 25 (see column 24, line 21) and SEQ ID NO: 34 (see column 18, line 20) under conditions whereby hybridization takes place between said probe and said rRNA or rDNA (column 2 to column 3), (2) observing or measuring detectable hybrids and relating the observation or measurement to the

presence of a target sequence of mycobacteria (column 2 to column 3). Hogan expressly teaches detection of mycobacterium tuberculosis (column 2, line 47) as well as other orgasnims such as intracellulare, and avium (column 2, lines 40-42). Hogan further teaches in vitro, in situ hybridization (column 1) as well as the use of a variety of samples such as sputum (column 66, line 53). Hogan further teaches signal amplifying systems such as enzymes or other non-isotopic labels (column 11).

Hogan does not teach the use of PNA probes.

Hyldig-Nielsen teaches the use of PNA backbones, including a backbone of the formula of claims 6, 15 and 18 (see page 17 of Hyldig-Nielsen) in probes for the detection of microorganisms using 16S rRNA base compositions (abstract). Hyldig-Nielsen expressly teaches that Z is NH, R2 is H, R3 is H, R4 is H, X and Y are O and Q is a nucleobase on page 17. Hyldig-Nielsen further teaches the use of labels and solid phase hybridization systems (page 3 and page 17). Hyldig-Nielsen further teaches the use of kits, which incorporate solid phase capture systems (page 45).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the PNA backbone of Hyldig-Nielsen in the hybridization method of Hogan since Hyldig-Nielsen teaches that

> "The present PNA probes form complexes with complementary nucleic acids which complexes are considerably more stable (higher Tm value) than would be a similar hybrid formed by a typically used nucleic acid probe of corresponding sequence allowing sensitive assays to be made with shorter probes than is the case of typical nucleic acid probes used today. Hybridization with traditionally used nucleic acid probes is much faster in solution than in solid phase hybridization. Due to the high affinity of PNA for nucleic acid, even solid phase hybridization between PNA

probes and nucleic acid can be performed rapidly allowing greater flexibility in assay format. Hybridization efficiency is only slightly influenced by pH and salt concentration in the hybridiation solution allowing PNAs to hybridize under conditions not favourable for ordinary DNA probes. Furthermore, PNAs have a higher thermal instability of mismatching bases wehreby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes of corresponding sequence would do (ref omitted). The structure of PNA is not degraded by nucleases or proteases making the PNA molecular very stable in biological solutions (page 3, line 21 to page 4, line 7)".

An ordinary practitioner would have been abundantly motivated to utilize the PNA backbone in the mycobacterial probes of method of Hogan in order to gain the advantages of improved stability, increased specificity, increased speed of hybridization, increased assay format flexibility, and improved resistance to nucleases.

Allowable Subject Matter

6. Claims drawn to methods using PNAs comprising SEQ ID Nos: 40, 44, 76, 89 and 90 would be novel and unobvious over the cited prior art.

Response to Arguments

7. Applicant's arguments filed July 5, 2002 have been fully considered but they are not persuasive.

Applicant argues that the reference of Hyldig-Nielsen teaches the use of PNA probes for a different purpose than that of the current claims. Hyldig-Nielsen teaches the use of PNA probes for the detection of microorganisms. Applicant appears to rely upon a difference between Mycobacteria and other organisms such as Neisseria in that the cell wall of Mycobacteria is more difficult to penetrate than other organisms such as

Neisseria. This argument is NOT commensurate in scope with the claim because none of the claims include a requirement that the probe penetrate the cell wall. Thus, this argument is irrelevant to the claimed invention. Currently, the method reads on detection of lysed cells, in which the cell walls of all of the organisms are burst or even where the nucleic acids are isolated from these organisms.

Thus, the argument of a teaching away is incorrect for two reasons. First, the scope of the claims do not support the argument. Second, there would still be motivation from Hyldig-Nielsen to assay any microorganism with PNAs. There is no express teaching away and the use of the PNA probes in a particular organism is not a teaching away. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Hyldig-Nielsen had a preferred embodiment, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from such embodiments such as those suggested by the Hogan reference.

Applicant then argues this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed.

Cir. 1988)." In this factual case, there is express suggestion in the prior art that the PNA nucleic acids are superior to DNA. There is further evidence as shown by Hyldig-Nielsen, that PNA actually function to detect nucleic acids in detection assays to detect microorganisms. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of PNA probes in detection of microorganisms. This is also not a situation where only general guidance was given. The prior art

provides specific guidance directing the use of PNA probes in the detection of microorganisms.

Applicant then appears to be arguing that unexpected results related to specific probes should be applied to the broader claims which are not limited to the specific probes. As MPEP 716.02(d) notes "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens , 622 F.2d 1029, 206 USPQ 289, 296 (CCPA 1980)." Here, there is no objective evidence that the scope of the unexpected results extends beyond the specific probes demonstrated to have unexpected results. Thus, the claim is not commensurate in scope with any argued unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

July 18, 2002